MEDICAL STAFF CONFERENCE

Anemia and Heart Failure

Association with Cardiomyopathy and Multiple Blood Transfusions

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* The association of anemia and heart failure always poses the very difficult therapeutic problem of whether blood transfusions will improve or worsen the heart failure. A patient in which this decision had to be made will be discussed today. The case will be presented by Dr. Stewart Spies.

DR. SPIES:† A 66-year-old Caucasian woman was admitted to Moffitt Hospital in January 1971 for evaluation of dyspnea during physical effort. She had been well until eight years ago when megaloblastic anemia was diagnosed. Vitamin B_{12} and folic acid therapy did not correct the anemia, and hemolysis and aplastic bone marrow developed. These complications required frequent and multiple blood transfusions. Several months before the patient was admitted to Moffitt Hospital a paroxysmal supraventricular arrhythmia developed and digitalis therapy was instituted. On physical examination the patient was observed to be chronically ill and icteric, with sinus tachycardia, cardiomegaly, a loud precordial systolic murmur, mild heart failure, increased pigmentation of the skin, and hepatosplenomegaly. Laboratory studies revealed anemia (hemoglobin 3.8 grams per 100 ml, hematocrit 14 ml per 100 ml) and a high serum level of iron (272 μg per 100 ml), chemical diabetes (fasting blood glucose 168 mg per 100 ml), and jaundice (total bilirubin 5.1 mg per 100 ml). Urinalysis yielded hemosiderin, but no blood was found in the stool. An electrocardiogram showed sinus tachycardia with occasional atrial premature beats and left ventricular hypertrophy. An x-ray film of the chest showed cardiomegaly with prominent pulmonary veins and other abnormalities compatible with congestive heart failure. Transfusion of four units of washed red blood cells was carried out and the hematocrit rose to 23 ml per 100 ml. The patient improved symptomatically and at present is free of breathlessness during physical effort.

DR. SMITH: We are fortunate to have Dr. Celia Oakley to discuss this case today.

DR. OAKLEY:* This patient had severe chronic anemia, congestive heart failure, and tissue hemosiderosis resulting from intravascular hemolysis and multiple blood transfusions. We shall discuss

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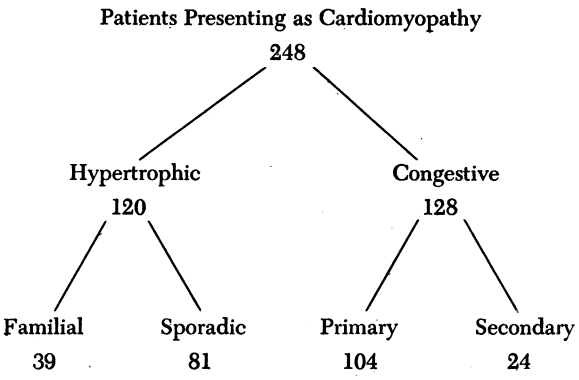
the etiologic features of her congestive heart failure and the adverse effects of anemia and transfusion hemochromatosis on cardiac performance.

In patients with chronic anemia, the red blood cell volume is decreased, the plasma volume is increased, and the total blood volume is usually within normal limits or low. The cardiac output is elevated, and there is a fall in peripheral vascu- and peripheral vasodilatation.[1] The vasodilatation is independent of the sympathoadrenal axis and teleologically it is assumed to result because the diminished oxygen-carrying power of the blood is not completely compensated by the increased blood delivery to tissues.[2] However, the real mechanism is unknown. The arteriovenous oxygen difference is narrow in patients with anemia, which indicates that the increased cardiac output is greater than it should be if the extraction of oxygen by tissue were complete. The increased output results from increased heart rate and stroke volume. These hemodynamic changes are also responsible for the murmurs that are so often heard in patients with chronic anemia.[3] These "flow-murmurs" arise in the outflow and inflow tracts of the right or left ventricles and manifest as precordial mid-systolic ejection or mid-diastolic murmurs, respectively. A third heart sound is also commonly heard. Cardiac dilatation seen on the x-ray film may result from the increased cardiac output and stroke volume or from heart failure. Experimental work has shown that cardiac output rises at hemoglobin levels between 4 and 9 grams per 100 ml but rarely at higher levels. When the hemoglobin falls below 4 grams per 100 ml, heart failure is common. Thus, in uncomplicated chronic anemia, heart failure is infrequently seen unless the hemoglobin value is below 4 grams per 100 ml.[4]

As evidenced by the wide arteriovenous oxygen difference between coronary arterial and coronary sinus venous blood, the oxygen extraction by the myocardium is almost complete. When the oxygen capacity is reduced in patients with anemia, myocardial hypoxia inevitably develops. Thus, in patients with severe chronic anemia the myocardium, particularly the subendocardial region of the left ventricle, is hypoxic, cardiac performance is impaired, and microscopic degenerative changes develop. Histologically, the myocardium, particularly the subendocardial surface, shows infiltration of fat. In older patients who have coronary artery disease, heart failure occurs at hemo-

TABLE 1.—*Cardiomyopathies Seen at the Royal Postgraduate Medical School, London, over a Ten-Year Period Ending December, 1970*



globin levels higher than 4 grams per 100 ml, and angina is common. The anginal syndrome may also occur in patients free of ischemic heart disease when severely profound anemia develops.[5]

In addition to the anemia, there was also the likelihood that the patient presented today may have had cardiomyopathy. Cardiomyopathy denotes a deficit in heart performance that is not a result of a valvular, congenital, hypertensive, or atherosclerotic disorder. Arrhythmias, including heart block, and cardiac failure are often the first manifestations of cardiomyopathy. Cardiomyopathy may be primary, if the process affects only the heart, or secondary, if the disease also affects other organs—for example, hemochromatosis. However, the underlying pathological process of cardiomyopathy is often ill defined, and such an idiopathic case is also termed primary cardiomyopathy. Naturally, semantic confusion arises when various series are then compared. At the Royal Postgraduate Medical School, London, we find a functional classification less confusing and clinically more useful (Table 1).[6] Hypertrophic cardiomyopathy is diagnosed when left ventricular hypertrophy is present, but left ventricular dilatation and heart failure are absent. Obstruction to left ventricular outflow is common at some stage in the disorder, with signs and symptoms similar to aortic valve stenosis. However, the treatment of idiopathic hypertrophic subaortic stenosis is medical, not surgical.

In familial hypertrophic cardiomyopathy, there appears to be a dominant inheritance with variable penetrance in the affected families. Familial hypertrophic cardiomyopathy does not differ clinically or hemodynamically from its noninherited

sporadic counterpart. Congestive cardiomyopathy accounts for the remainder of the primary and secondary cases and is diagnosed when heart failure is present. A specific cause of the heart failure is found in only a minority ofpatients. When associated disease is found in other organs, secondary cardiomyopathy is diagnosed; all secondary forms are also congestive.

Hemodynamically, in congestive cardiomyopathy the cardiac output and ejection fraction is low and the residual volume and ventricular filling pressures are elevated. Clinically, breathlessness, edema, and a dilated or "baggy" left ventricle are present. Etiologically, congestive cardiomyopathy is infective, toxic, metabolic, endocrine, collagen-vascular, neurological, hematological, degenerative, or senile in origin.

When no cause is found, a previous viral infection is the most probable. However, it is curious that chronic myocardial failure develops so infrequently in patients with proved acute viral myocarditis. In the few cases in which acute viral myocarditis does "progress" into chronic myocardial failure, all signs of the viral infection disappear. Alcoholic cardiomyopathy is also common, but it may be that alcohol exacerbates and triggers a previous myocardial abnormality rather than effects chronic myocardial failure per se. Prepartum cardiomyopathy is common in parts of the world where poverty and low standards of living are rife and specific nutritional deficiencies or toxins have not yet been identified.

Blood disorders account for a small proportion of secondary types of cardiomyopathy. Polycythemia and microangiopathic hemolytic anemia are associated with vascular occlusions, the former with venous thrombosis and coronary arterial occlusions and the latter with obstruction by split fibrin products in the small arteries in the heart, brain and kidney. Amyloid deposition associated with multiple myeloma is also a cause of myocardial infiltration and congestive heart failure. In patients with hemochromatosis, the tissue iron stores are increased and heart failure may occur. Deepening of skin color, diabetes, hepatosplenomegaly, and jaundice may all be present; bronze diabetes is an apt synonym for the entity. An elevated level of iron in the serum and hemosiderin in the urine strongly suggest the diagnosis, but a definite diagnosis can only be made when tissue damage is documented by histological examination of a biopsied liver specimen. Recently, however, a characteristic urine iron response to deferoxamine methanesulfonate (Desferal®) has been described[7] as confirmatory, obviating the liver biopsy.

TABLE 2.—*Classification of Hemochromatosis

I. Idiopathic—develops in absence of known causes of iron overload; often family history of iron storage disease
   - A. Prefibrotic stage; increased stores and absorption with a positive family history
   - B. Fibrotic stage—organ damage

II. Secondary—(more common than idiopathic)
   - A. Chronic hemolytic anemias
   - B. Repeated blood transfusions for aplastic anemia
   - C. Alcohol ingestion with excess dietary iron (Bantu hemochromatosis)
   - D. Congenital defects in iron metabolism leading to iron loading; for example, transferrin deficiency, thalassemia major, and pyridoxin-responsive anemia

*Tissue damage with increased total body iron stores (assessed by tissue biopsy and response to repeated venesection or chelating agents).

Congestive heart failure or arrhythmia develops in 30 percent of patients with hemochromatosis. Increased iron stores and fibrosis involving the myocardium are likely responsible for the congested state, but heart failure may also be related to an impairment of enzyme systems, especially those of the glycolytic cycle, a block in xanthine oxidase production or an impairment of myoglobin synthesis.[8,9,10,11] In patients with idiopathic hemochromatosis anemia is not present, but parenchymal stores of iron are increased and when accompanied by fibrosis are pathogenic for congestive heart failure due to hemochromatosis.[12,13]

In hemosiderosis, the reticuloendothelial stores of iron are increased and fibrosis and heart failure are not present.[14] Hemolytic anemia and repeated transfusion of blood give rise to secondary hemochromatosis or secondary hemosiderosis (Table 2).[15] When heart failure develops in a patient who requires frequent multiple blood transfusions for chronic refractory anemia and when the hematocrit is 25 per cent or greater, a working diagnosis of transfusion hemochromatosis is legitimate.[16] Sickle cell anemia is a classic exception to this rule and heart failure often occurs in the absence of hemochromatosis.[17] Interestingly, heart murmurs in these patients are often incorrectly diagnosed as evidence of rheumatic heart disease. Treatment of hemochromatosis is re-

peated venous phlebotomy. The objective of therapy is to decrease tissue iron stores, which hopefully prevents continuation of tissue fibrosis. Since phlebotomy is impractical in patients with refractory anemia, iron-chelating agents are used; however, to date, this approach has been disappointing.

The patient presented here has cardiac infiltration with iron, but she is not considered to have cardiac hemochromatosis. Heart failure developed only when the hemoglobin level was less than 4 grams per 100 ml, that is, when she became severely anemic. Furthermore, the congestion developed years after diagnosis and treatment of megaloblastic anemia by repeated blood transfusions and was easily reversed by elevation of the level of hemoglobin. Heart failure, therefore, was induced by the severe anemia. However, the increasing amounts of iron in her heart may lead to eventual cardiac fibrosis and transfusion-effected heart failure, although the time course of this process cannot be forecast. To date, it is not possible to establish a correlation between the duration and severity of hemolytic anemia and the number of blood transfusions required for ultimate development of the myocardial incapacity.

TRADE AND GENERIC NAMES OF DRUGS

Desferal® .....deferoxamine methanesulfonate

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SURGICAL TREATMENT OF OPEN-ANGLE GLAUCOMA

What are your criteria for surgery in chronic open-angle glaucoma?

"I use the classic criteria. If visual field loss is progressing, despite the best tolerable medical therapy, surgical therapy is indicated.

"Let me make just a point about this field loss progression. I think it is extremely important to emphasize that visual field testing must be done with the pupils at least fairly well open because false field defects and some which simulate classic glaucomatous defects surprisingly well can be produced by miosis alone and particularly by miosis if there is early or incipient cataract present. So don't hesitate to dilate the pupils to test the visual fields in these people. In our hands, the drug Mydriacyl® has been the best thing for counteracting even the strong miotics, the strong anticholinesterase drugs that we've had before. It will open the pupils quite quickly even in the face of these drugs. Of course, it doesn't keep them open very long, so it's an excellent drug to use.

"If with the open pupils we get field loss with an isopter comparable to the 2 to 1,000 or a comparable isopter on the Goldman perimeter (which we increasingly like to use for our final judgments), we will go ahead with filtering surgery in the chronic open-angle glaucoma."

—Panel Discussion, The Need for Therapy in Glaucoma
Extracted from *Audio-Digest Ophthalmology*, Vol. 7, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057